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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,861	03/21/2005	Kenichiro Kosai	042-301	9980

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APEX JURIS, PLLC
TRACY M HEIMS
LAKE CITY CENTER, SUITE 410
12360 LAKE CITY WAY NORTHEAST
SEATTLE, WA 98125

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,861	KOSAI ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1-34 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-03-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1-36 are currently pending. Claims 1-13 and 24-33 have been amended and claims 36 and 37 have been canceled by Applicant's amendment filed on 12-03-2007. Claim 35 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species pursuant to 37 CFR 1.142(b) there being no allowable generic or linking claim.

Response to Restriction Requirements

On page 8 of Remarks, Applicants' argue that "anywhere in the election/response office action received from the Examiner, nor in the Applicant's response to the election/restriction where the Applicant is requested to or does withdraw Claim 35. Therefore, Applicant respectfully requests that Claim 35 be returned to the claims listing for consideration". Such is not persuasive.

Claim 35 was withdrawn from consideration in the previous office action filed on 07-02-2007 (see Detailed action page 2) in response to the species election made by Applicants in the response filed on 04-09-2007, wherein Applicants elected the Nkx2.5 gene as the promoter in the second recombinant DNA, as recited in claim 7. Therefore claim 35 drawn to an αMHC as the alternative promoter for the second recombinant DNA was withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species there being no allowable generic or linking claim. The examiner notes that claim 35 was inadvertently left out in the

Office Action Summary PTOL-326 Form, however claim 35 was clearly withdrawn from consideration as pointed out at page 2 of the previous office action filed on 07-02-2007.

3. Therefore, claims 1-34 and 36 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Rejections withdrawn in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112

In view of Applicants' amendment of claims 1-13 and 24-33 to introduce the limitation "in vitro" rejection of claims 1-34 and 36 under 35 U.S.C. 112, first paragraph, has been withdrawn. Reconsideration of search results in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing discloses sufficient enablement for *in vitro* manipulation of embryonic stem cells

Rejections maintained in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 103

Claims 1-8, 11, 14-18, 21, 24, 27, 30, 33, 34 and 36 remain rejected under 35 USC 103 as being unpatentable Vallier et al, (PNAS, 2001, 98:2467-2472) in view Ong et al., US Patent No: 6,777,235, Date or Patent Aug. 17, 2004) and further in view of Rybkin et al., (Biol. Chem., 15927-15934, 2003).

Reply to applicant arguments as they relate to rejection of Claims 1-8, 11, 14-18, 21, 24, 27, 30, 33, 34 and 36 under 35 USC § 103.

In relation to the Vallier et al., reference, Applicants argue at page 9 of Remarks, that "Although the reference shows an increase in the number of positive cells of EGFP (at Table 1), there is neither description nor suggestion about elevating the expression intensity of EGFP, as is disclosed in the present invention". Such is not persuasive.

The Vallier's reference discloses an *in vitro* method for selectively isolating and visualizing embryonic stem cells after transfection with a vector encoding the EGFP under the control of a constitutively activated promoter. The vector taught by Vallier et., teaches all the limitations of the first recombinant DNA embraced by the instant invention. Moreover, Applicants argue limitations that are not present in the claims. The claims recite "a first recombinant DNA in which a first promoter, a gene having recombinase recognition sequences on both ends and a fluorescence protein gene". There is not limitation to any elevation of expression intensity of EGFP in the instant claims.

In relation to the Rybkin reference, Applicants contend that 'the Cre system is not used for *in vitro* differentiation of ES cells, but rather it is used for producing a transgenic mouse. This is an *in vivo* usage of the Cre system. In other words, in Rybkin the Nkx2.5 acts on the embryologic stage in the fetus of the mouse. Alternatively, in the present invention, Nkx2.5 acts on *in vitro* differentiation of ES cells. This is entirely different." Such is not persuasive.

Rybkin discloses the construction of a DNA vector wherein expression of a Tag gene is under the control of a Nkx2.5 gene. The fact the DNA construct is used to generate transgenic mice carrying the Nkx2.5 cardiac specific regulatory sequence is irrelevant to the specifity of Nkx2.5 as a marker of cardiogenesis. There is not reason to believe that a promoter that is tissue specific for cardiocytes *in vivo* would not regulate *in vitro* transcription in the same cell type.

Indeed, Rybkin discloses at p. 15928, col. 1, paragraph 2, that "recently, a cardiac cell line that expresses Tag under the control of the proximal cardiac enhanced of the Nkx2.5 gene was derived". Hence the teachings of Rybkin complement the disclosure of Vallier et., and Ong et al., by teaching the Nkx2.5 promoter as a marker of cardiogenesis.

At page 9 of Remarks, Applicant argue that in " Rybkin and Ong, the DNA of interest is integrated to target cells. However, the work to achieve strain by integration requires an excessive amount of time and is also extremely labor intensive. Moreover, if integration of DNA of interest is used for in vitro differentiation of ES cells, it is well known that the structure of chromosome is influenced and the expression of gene is unstable and shut off". Moreover, Applicants contend that "the present invention is not integrated by introducing arbitrary promoter into Cre-expressing adenovirus. Therefore, in the present invention the labor and time needed are remarkably reduced for producing the Cre expression adenovirus which this promoter is introduced into. Moreover, in the present invention, since the introduced gene of interest is maintained in the cell nucleus under episomal conditions, this gene is stable and the expression of this gene is not influenced by the host's chromosome". Such is not persuasive.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Furthermore, with respect to applicants' argument that, " the introduced gene of interest is

maintained in the cell nucleus under episomal conditions, this gene is stable and the expression of this gene is not influenced by the host's chromosome" is not found persuasive because it is noted that the features upon which applicant relies (i.e., gene of interest is maintained in the cell nucleus under episomal conditions, Specification, page 40) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite the advantages of using adenovirus taught in the specification.

Claims 1-6, 8-34 and 36 are rejected under 35 USC 103 as being unpatentable Vallier et al, (PNAS, 2001, 98:2467-2472) in view Ong et al., US Patent No: 6,777,235, Date or Patent Aug. 17, 2004) and Rybkin et al., (JBC 2003, 15927-15934) as applied to claims 1-8, 11, 14-18, 21, 24, 27, 30, 33, 34 and 36 above and further in view of Yamamote et al., (Oncogene 2002, 899-908).

Reply to applicant arguments as they relate to rejection of Claims 1-6, 8-34 and 36 under 35 USC § 103.

In relation to the Yamamote et al., Applicants contend that the "the Cre-expressing adenovirus are used for *in vivo*. However, the present invention is used for *in vitro*. The Cre-expressing adenovirus of the present invention also differs from those disclosed in Yamamoto. Therefore, as set out above, the present invention would not have been motivated by the references cited". Such is not persuasive.

Yamamote et al., complements the teachings of Vallier et al, Ong et al., and Rybkin by teaching delivery and coditional expression of a gene of interest using as first recombinatn DNA as an adenovirus vector. Moreover, as disculsed in the parargraph above, there is not reason to believe that an *in vivo* delivery of a target molecule using an adenovirus vector would not work *in vitro*. Conversely, *in vitro* delivery by an adenoviral vectors would not necessary be successful *in vivo* as the barriers encountered by said vector are more complex *in vivo* than in the culture system.

Conclusion

Applicant response filed on 12-03-2007 has been fully considered but has not been found persuasive in overcoming the grounds of rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Maria Leavitt, PhD
Patent Examiner P/1633
Remsen 2B55
Phone: 571-272-1085

/Anne Marie S. Wehbe/

Primary Examiner, Art Unit 1633